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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/771,774	02/04/2004	Hubert Barth	PC20545A	4105

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
06/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

	Application No.	Applicant(s)	
Office Action Summary	10/771,774	BARTH ET AL.	
	Examiner	**Art Unit**	
	Tamthom N. Truong	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3-10-07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment of 3-10-07 has been fully considered. The argument has overcome the previous rejections of 112/1st and 2nd paragraphs regarding the description of "ester, amide or prodrug thereof". However, there is still an issue of enablement regarding how to make such a prodrug by the reaction scheme recited in the instant claims as discussed below.

Applicant's argument has not overcome the previous 103 rejection based on **Small et. al.** in view of **Himmelsbach et. al.** (US'634). Therefore, said rejection is maintained herein as discussed below.

Claims 1-11 are pending.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. **Scope of Enablement:** Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a compound of formula I, does not reasonably provide enablement for a method of making an "*ester, amide or prodrug thereof*". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these

claims. The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;

(2) The amount of direction or guidance presented;

(3) The state of the prior art;

(4) The relative skill of those in the art;

(5) The predictability or unpredictability of the art;

(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claim 1 recites a method of making a compound of formula I, and optionally converting it to a pharmaceutically acceptable salt, ester, amide or prodrug thereof. The scope of "prodrug" is briefly defined on page 14 of the specification by reference to a text book,which includes a myriad number of esters and amides or other functional groups on formula I. Furthermore, such an ester or amide could be placed anywhere on the compound of formula I. Thus, the scope of claim 1 and dependent thereon is unduly broad.

The amount of direction or guidance presented: Applicants asserted that "the specification describes numerous examples and methods of preparing esters, amides and prodrugs..." However, no such working example is found. The compound itself has an amide side chain of "acrylamide", which is not the ester or amide of a prodrug. The general teaching and examples are directed to a process of making the (active) compound itself, not its prodrug.

First, the specification does not discuss the preferred functional group, and its site on the compound for a prodrug. Second, the specification does not describe the starting material for making a prodrug. Third, the specification does not show the additional step and/or reagent for adding a functional group to the compound to obtain a prodrug. Thus, the specidication fails to provide a process for making such an ester, amide or prodrug of the claimed formula I.

The state of the prior art: Although it is not unusual to expect a "prodrug" of a compound, the process for selecting a particular ester, amide, phosphate, sulfate, hydrate or solvate is not standard for all drugs. As evident by the teaching of **Himmelsbach et. al.** (US'634 – cited previously), the process of making a prodrug of an analogous compound of formula I is not the same as the process of making the active compound itself. Obviously, additional starting materials and reaction conditions are required which are not taught by Himmelsbach et. al. Thus, the state of the art does not provide sufficient guidance for a process of making an "ester, amide or prodrug" of the claimed compound.

The relative skill of those in the art: Even with the advanced training, the skilled clinician would have to engage in extensive research to select a particular "prodrug" for each compound from the large Markush group of the instant formula I. Not only one would have to obtain appropriate starting materials, but additional step for adding the desired functional group for each "prodrug". Given a large Markush group of the three formulae, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The process of making a prodrug requires three criteria: (1) the "prodrug" must be

biologically inactive; (2) the "prodrug" must be metabolized into the active drug at a physiologically meaningful concentration; (3) the active drug must still have the intended biological activity. Many prodrugs produce additional active metabolites (*in- vivo*) that do not have the same chemical structure of the intended drug. Thus, the process of making a prodrug is highly unpredictable due to many unknown *in-vivo* factors as well as uncertain numbers of active metabolites with potential adverse effects.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

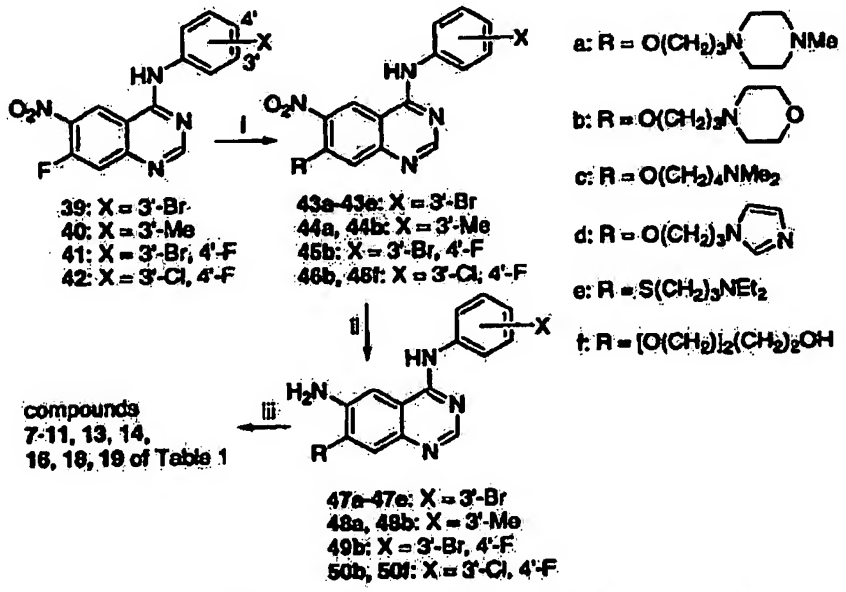
2. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Small et. al.** in view of **Himmelsbach et. al.** (US'634), and **Barth et. al.** (US 6,66,390 B2) or **Rewcastle et. al.** (J. Med. Chem., 1996, Vol. 39, pp. 918-928) – both are newly cited. The rejection is reinterated as below:

On page 1381, Scheme 2 Small describes a general process of making compound #18 (which is the same compound recited in the instant claim 11). Page 1390 details the process of making such a compound. Note, the term "comprising" in claim 1 does not exclude any steps leading up to formula 10. The disclosed multi-step process only differs from the claimed process by not having a G (or protecting) group on the amino (of the anilino).

Scheme 2[a]



[a] (i) RO^-Na^+/THF/reflux/18–24 h or RS^-Na^+/DMSO/65 °C (for 39–43e) or RO^-K^+/DMSO/25 °C (for 42–46f); (ii) Fe/AcOH/EtOH/H_2O/reflux/20 min or H_2/Pd–C/MeOH:EtOAc (2:1) (for X = 3'-Me) or H_2/Raney Ni/THF (for 46f); (iii) CH_2=$CHCO_2H$/EDCI·HCl/pyridine or Et_3N/DMA or DMF/2 h or (for 50f) CH_2=$CHCO_2H$/*t*-BuOCOCl/Et_3N/THF.

Note, the above reaction also teaches the reduction step (step II – converting NO_2 to NH_2) which suggests the process recited in the instant claim 3. The replacement of the leaving group at the 7-position recited in the instant claim 5 is also taught in step I of the above scheme.

Barth et. al. and Rewcastle et. al. are applied to show early formation of precursors covered in the instant claims 3-6, especially claim 6 which is discussed in Method B on page 919 of Rewcastle, and columns 2 (line 39) to column 3 (line 13) in Barth et. al.

The difference of lacking a protecting group (G) can be overcome by the teaching of Himmelsbach et. al. On columns 10-13, Himmelsbach et. al. describe a generic process of making a quinazoline compound with analogous substituents at the 4th, 6th and 7th positions. Then, on column 13, Himmelsbach et. al. discuss the possibility of having a protecting group on the amino, see the following excerpt:

> In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, amino, alkylamino, or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.
>
> For example, a protecting group for a hydroxy group may be a trimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert-butyl, trityl, benzyl, or tetrahydropyranyl group,
>
> protecting groups for a carboxy group may be a trimethylsilyl, methyl, ethyl, tert-butyl, benzyl, or tetrahydropyranyl group, and
>
> protecting groups for an amino, alkylamino, or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert-butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxy-benzyl, or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.
>
> Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g., in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water, or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid, or sulfuric acid, or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide, or aprotically, e.g., in the presence of iodotrimethylsilane, at temperatures between 0° C. and 120° C., preferably at temperatures between 10° C. and 100° C.

Note, not only does Himmelsbach et. al. disclose several protecting groups for an amino, but they also reveal reagents or reaction conditions to cleave such a group. Thus, the addition of the protecting group G recited in claim 4 is suggested in the above passage.

Applicants argued that: "Although the passage relates to protecting groups, the Examiner does not provide any motivation in Small and/or Himmelsbach to suggest the claimed process of the instant application. It is submitted that the rejections under 35 USC § 103(a) are based on speculation or the unsupported opinion of the Examiner derived by hindsight knowledge of Applicant's specification since there is n teaching or suggestion in the references to make the combinations alleged by the Examiner to be obvious."

The motivation, of course, comes from the teaching of Himmelsbach in recognizing the need to protect a **reactive amine group.** In the instant process, the reactive amine group is the the one at the 4-position. It would have been within the level of one skilled in the art to appreciate which amino group should be protected to increase the yield of desired 6-acylatedamino product.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See ***In re McLaughlin***, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Thus, with the teaching of Himmelsbach et. al., the skilled chemist would have been motivated to modify the process of Small, Barth & Rewcastle by having a protecting group on the amino (of the anilino).

Therefore, it is maintained that the instant process of making a compound of formula I would have been obvious in view of the combined teachings above.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tamthom N. Truong whose telephone number is 571-272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Tamthom N. Truong
Examiner
Art Unit 1624

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5-21-07

EMILY BERNHARDT
PRIMARY EXAMINER
GROUP 1600

Notice of References Cited	Application/Control No. 10/771,774	Applicant(s)/Patent Under Reexamination BARTH ET AL.	
	Examiner Tamthom N. Truong	Art Unit 1624	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-6,664,390	12-2003	Barth et al.	544/119
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	REWCASTLE, G.W. et. al., "Tyrosine Kinase Inhibitors..." J. Med. Chem., 1996, Vol. 39, pp. 918-928.
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

5/21/07